Pharmaceutical Intermediates

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Summary

Total European chemical production grew by 3.3% over the period 1999-2004. Primary driving force of this increase was the pharmaceutical ingredients or pharmaceutical intermediates segment. The German Chemical Industry Association (VCI) estimated German pharmaceutical ingredients production in 2004 at EUR 24.4 billion. The basic pharmaceuticals segment amounted to approximately 10% of this market or, EUR 2.4 billion.

Worldwide growth in the pharmaceutical intermediates segment is estimated at 4-6% annually. In Germany, growth rates of 4-5% per year are expected for the period of 2005-2007. Certain products, such as chiral substances, where competition from Asia is limited, could experience higher growth rates.

The structures of the pharmaceutical intermediates markets in Germany and Europe are similar. They are highly international and dominated by direct purchase and custom-synthesis activities. Distributors are of minor importance. End-users are the global pharmaceutical players, which select production sites for their intermediates close to sales markets. With the exception of standard intermediates, which are quite price sensitive, quality is the main buying factor for special, often custom-synthesized intermediates.

Market Overview

The German Pharmaceutical Basic Substances Market (EUR Billion)

				Est. Avg. Annual
	2003	**2004**	**2005 (est)**	**Growth (%)**
				2006-2008
Imports	3.27	3.18		3.5
Production	2.40	2.10		2-2.5
Exports	3.60	3.18		
Total Market	**2.07**	**2.1**		**4**
U.S. Imports	0.88	0.64		4

Official German statistics do not distinguish between pharmaceutical intermediates and basic pharmaceutical substances. Actual pharmaceutical intermediates market values should be higher than the above statistics, as pharmaceutical intermediates are registered only if they are taken out of the production process and sold. In reality, however, pharmaceutical intermediates often continue in the production process until they become an active pharmaceutical ingredient (API) or a drug.

With continuing healthcare reforms in Germany, pharmaceutical producers are increasingly facing extra costs. In view of the financial burdens generated through the German healthcare system and the competition from Asia in the field of standard intermediates, producers reduced over-capacities and restructured their businesses over the past few years. 2004 saw a decrease in domestic production and total imports, including U.S. imports, compared with 2003. For 2005, experts are cautiously optimistic, especially since European intermediates producers concentrate on the development of new technologies, and special niche markets; developing products with which Asian or Indian firms cannot easily compete. Products for which pricing is not a major competitive factor, such as exclusive synthesis and innovative intermediates may see slightly higher growth rates, about 4-5%, than standard intermediates facing competition from China and India.

The intermediates market is driven mainly by drug demand. The German Association of Researching Drug Producers (VFA) lists 253 pharmaceutical research projects that may lead to new drugs by 2007. New molecular entities (NME) are the main bases for new active pharmaceutical ingredients (APIs) or the replacement of a formerly less effective ingredient type. An increase of NMEs ultimately leads to new pharmaceutical intermediates. In 2004, 35 NMEs were introduced into the German market, the largest number of NMEs in Germany since 1998; 11% of them were genetically generated.

The following lists the new pharmaceutical substances that entered the German market in 2005 and 2004. The individual substance's name is linked which information on molecular/structural details (detailed molecular descriptions are only available in German).

New Pharmaceutical Substances in Germany (2005)	
Substance Name / Trade Name	**Group**
Anagrelid (Xagrid®)	Antihaemorrhagic
Atomoxetin (Strattera®)	Psychopharmacologic
Bevacizumab (Avastin®)	Cytostatic
Ciclesonid (Alvesco®)	Broncholytic
Darefenacin (Emselex®)	Urologic
Loteprednoletabonat (Lotemax®)	Ophthalmic
Nitisinon (Orfadin®)	Enzymes
Palonosetron (Aloxi®)	Anti-emetic
Paricalcitol (Zemplar®)	Osteoporosis
Zonisamid (Zonegran®)	Anti-epileptic

New Pharmaceutical Substances in Germany (2004)	
Substance Name / Trade Name	**Group**
Aripiprazol (Abilify®)	Psychopharmacologic
Atazanavir (Reyataz®)	Antibiotic / Chemotherapeutic
Bivalirudin (Angiox®)	Anticoagulant
Bortezomib (Velcade®)	Cytostatic
Carglumsäure, (Carbaglu®)	Enzymes
Cetuximab (Erbitux®)	Cytostatic
Cholera-Toxin-B (Dukoral®)	Sera
Cinacalcet (Mimpara®)	Osteoporosis
Duloxetin (Yentreve®)	Urologic
Efalizumab (Raptiva®)	Dermatologic

Eflornithin (Vaniqa®)	Dermatologic
Eplerenon (Inspra®)	Diuretic
Epinastin (Relestat®)	Ophthalmic
Etoricoxib (Arcocia®)	Analgetic/Antirheumatic
Everolimus (Certican®)	Immune modulator
Fosamprenavir, (Telzir®)	Antibiotic/Chemotherapeutic
Fulvestrant (Faslodex®)	Cytostatic
Insulindetemir (Levemir®)	Antidiabetic
Insulinglulisin (Apidra®)	Antidiabetic
Levobupivacain (Chirocain®)	Local anaesthesia
Manidipin (Manyper®)	Calcium channel blocker
Melagatran Injektionslsg., Ximelagatran (Exanta®Tablets)	Anticoagulant
Nadifloxacin, (Nadixa®)	Dermatologic
Olopatadin (Opatanol®)	Ophthalmic
Pemetrexed (Alimta®)	Cytostatic
Porfimir Photofrin	Cytostatic
Pregabalin (Lyrica®)	Anti-epileptic
Racecadotril (Tiorfan®)	Gastro-enteric
Solifenacin (Vesikur®)	Urologic
Strontiumranelat (Protelos®)	Osteoporosis
Yttrium-90-marked Ibritumomab-Tiuxetan, (Zevalin®)	Cytostatic

Source: Pharmaceutical Journal, Eschborn/Germany

Market Trends

Outsourcing pharmaceutical companies expect suppliers who offer special intermediates to also be able to provide standard intermediates production processes, as a proof of the producer's expertise. In addition, it is of advantage if intermediates suppliers offer a broad technological portfolio enabling them to process a substance through various stages of chemical transformation. Occasionally, large pharmaceutical firms spread new drug projects among several independent suppliers to assure that the full drug recipe remains confidential. The multi-national and trans-global enterprises continue to outsource their raw materials and intermediates on a global basis to minimize material cost and to assure that their suppliers are close to production facilities. The trend towards mergers and acquisitions is likely to continue, as are partnerships among large producers, such as the one between BASF and Solvias in the field of ligands.

Well-established standard fundamental processes like hydrogenation and alkylation are subject to strong price competition. The trend of price under-cutting by Asian and Indian intermediates producers will continue, particularly where "primitive" intermediates, subject to less stringent production regulations, are concerned. Increasingly, Asian firms are able to comply with Good Manufacturing Practices (GMP) standards required for the production of more sophisticated intermediates.

Emerging Market: Chiral Substances

Chiral substances have become important. Insiders consider the chiral substances segment as best prospects market. They expect the global market for chiral pharmaceutical substances and intermediates to increase to EUR 15 billion by 2009,

nearly doubling its market value from 2002. Today, 86% of all pharmaceutical substances introduced into the market are chiral. Enantiomers exist in two forms, one of which is only therapeutically active while the other may cause adverse effects. This is why today's pharmaceutical firms prefer to have only the therapeutically active form in a substance. Industry requires the chiral materials for the synthesis of optically- and enantiomer-pure pharmaceutical substances. German intermediate producers are increasingly focusing on the production of chiral substances.

End-Users

The German population is getting older. Since an elderly population generally requires more medication, this trend would, in the medium-term, result in additional demand of drugs (and intermediates) needed for the elderly people, i.e., diabetic drugs like Humulin. The streamlining of processes and the reduction of production costs will continue as will the trend towards more sophisticated intermediates. Research increasingly focuses on molecular structures. Biotechnologically produced and genetically modified substances are on the advance. In August 2004, 106 genetically modified drugs with 77 different substances were on the German market. Moreover, phyto-pharmaceutical ingredients such as, for example, alkaloids made from plant extraction, are expected to grow in importance. Today, chiral building blocks are an integral part of drug development. Manufacturers of chiral substances have to possess the necessary technology and have to have a high amount of experience. Suppliers include: Avecia; Degussa; DSM; Lonza; Wacker Fine Chemicals; and others.

End users of intermediates are:

Pharmaceutical companies, for in-house completion of APIs;
Active pharmaceutical ingredient manufacturers;
Other downstream producers.

In the past, the large pharmaceutical firms put pressure on their intermediates suppliers with whom they maintain close relationships, to obtain price-competitive products and secure profits. Because of secrecy concerns, pharmaceutical firms often use several intermediates suppliers. Sometimes, they even prefer to manufacture the process-oriented intermediates themselves. The more standard-type pharmaceutical intermediates are purchased or production is contracted out.

Import Market

EU market players appreciate the quality of U.S. products and their high standards as set forth by the FDA. They are reportedly concerned about increased imports of intermediates from Asia, which often do not comply with the existing GMP manufacturing standards in Europe and other industrialized countries.

Following is an overview of German imports of pharmaceutical basic substances from the United States in 2004.

Major German imports from the United States (volume in tons)

2923 20 00	Lecithin and other phosphor amino lipoids	6,715,500
2922 41 00	Lysine (ester salts)	3,617,200
2923 90 00	Quaternary organic ammonium salts	3,145,200
2924 19 00	Acyclic amides and its derivatives	3,076,300
2940 00 00	Chemically pure sugars	1,354,000
2932 29 80	Lactones	1,103,500

Major German imports from the United States (value in EUR million)

2923 20 00	Lecithin and other phosphor amino lipoids	EUR 4.9
2922 41 00	Lysine (ester salts)	EUR 6.3
2923 90 00	Quaternary organic ammonium salts	EUR 6.4
2924 19 00	Acyclic amides and its derivatives	EUR 6.6
2924 29 95	Cyclic amides incl. cyclic carbamat	EUR 5.8
2932 29 80	Lactones	EUR 11.0
2933 59 95	Pyrimidine-piperazine ring compounds	EUR 6.7
2935 00 90	Sulfonide	EUR 4.5
2936 28 00	Vitamin E and derivates	EUR 10.7
2937 21 00	Cortisone hydrocortisone etc.	EUR 2.7
2937 29 00	Hormones, steroids	EUR 265.8
2941 90 00	Antibiotics, other	EUR 6.2
3002 90 50	Cultures of micro-organisms	EUR 7.3

Source: German Federal Statistics Office

Market Access

The pharmaceutical intermediates market is dependant not only on market conditions and market demand, but also on local health policies such as the Healthcare Reform in Germany. As a result of the reforms in Germany, drugs prescribed by the Statutory Health Insurance are subject to a so-called "Herstellerrabatt," a manufacturers' discount to pharmaceutical wholesalers on prescription drugs. As of January 2005, the discount amounted to 6%, down from 16% in 2004. However, a pharmaceutical company holding a patent for an OTC product can still set the price based upon its own considerations and the market value of the product.

Pharmaceutical intermediates producers include SMEs, offering services and selected niche technology processing steps; KMUs which are usually generalists with a diversified chemical portfolio and technological competences; and large corporations, mostly the pharmaceutical global players, seeking to reduce overcapacities. Furthermore, there are over 28 chemical Contract Manufacturing Organizations (CMOs) in Germany, offering contract manufacturing of intermediates. Additional information is available at: http://www.casid.de

Intermediates are usually sold directly to the end-user, in most cases the pharmaceuticals manufacturer. The substances are often produced exclusively either by a specialized CMO or by a chemical producer. Only 10-20% of intermediates are supplied by distributors. Building block intermediates often originating from China and India, are marketed through distributors.

Competitive Factors:

- Pricing
- Quality
- Speed of delivery
- GMP compliance

The closer the production process comes to the target active ingredient, pricing is replaced by quality and purity considerations.

The German and other European pharmaceutical markets are highly regulated. From the regulatory standpoint, treatment of an intermediate and an active pharmaceutical ingredient differs. While intermediates are less stringently regulated, GMP (Good

Manufacturing Practice) observance for APIs is considered a proof of high quality and preferred. The EU Directive 2004/27/EC coming into force in October 2005, amending Directive 2001/83/EC, will include some additional substances that were formerly not subject to the GMP requirement. Production according to GMP is necessary for all pharmaceutical ingredients of human drugs. It will also apply to certain excipients in the future.

Further information on GMP relating to drugs, APIs and intermediates "considered as API starting materials," other than those produced by chemical synthesis, is available in Annex 18 of the EU' s Good Manufacturing Practice Guidelines:
http://pharmacos.eudra.org/F2/eudralex/vol-4/home.htm

In Germany, the approval of drugs, APIs and their starting materials (unless they are solely based on chemical synthesis), is obtained in advance by a manufacturer - either the pharmaceutical company or the intermediates producer. In addition, intermediates producers can obtain a quality certificate from EDQM (European Directorate for the Quality of Medicines) signifying that production and testing comply with the respective EU legislation. http://www.pheur.org/site/page_625.php

Imports from the United States would basically be treated like domestic products. The following products need a GMP certificate and may be subject to inspection: Any API or substance which contains the structural basics of an API, or constitutes a pre-stage of an API, which is not solely produced by simple chemical synthesis but contains human, animal, genetic or micro-biological or any other substance of human origin.

Competitive Situation

Particularly in the field of standard intermediates, it is difficult for small firms to compete with large producers who can offer considerable discounts. The intermediates market is dominated by firms operating internationally.

Major Producers of Intermediates are:

Aerojet Fine Chemicals, Air Products and Chemicals, Albemarle, Archimica/BTP, Ascot, Atofina, Avecia Fine Chemicals, BASF, Borregaard Synthesis, C6 Solutions, Cambrex, ChemFirst Fine Chemicals, Chemetall, Clariant, Contract Chemicals, CU Chemie Uetikon, Degussa, Dow, DSM, Dynamic Synthesis, Eastman, EMS Dottikon, Finorga, Great Lakes, Honeywell, Inspec, ISP, Kemira, Koei Chemical, Laporte, Lonza, Omichem, PCAS, PPG Fine Chemicals, Procos, Reilly, Rhodia, Ruetgers Organics (soon Wylchem), SF-Chem, Siegfried, Sigma-Aldrich, SKW Trostberg, SNPE, Sumitomo Seika, Tessenderlo, Wacker Fine Chemicals, Yule Catto etc.

Source: Jan Ramakers Fine Chemicals Consulting Group, various

Mergers, Acquisitions, Partnering Activities

- In January 2005, Wacker Group spun off its fine chemicals, exclusive synthesis and biotech sections into a separate business unit named Wacker Fine Chemicals.
- Lanxess plans to reduce its workforce in the fine chemicals unit and regroup it into a separate business unit. It also plans to expand its fine chemical activities in Spain.
- The acquisition of Orgamol by BASF is nearly accomplished. Approval by the Anti-Trust Authorities is expected soon. Orgamol is one of Europe's major CMOs for pharmaceutical intermediates, focusing on halogenation (total annual sales in 2004: EUR 100 million).

- In 2004, Rockwood Specialties Group acquired four Dynamit Nobel companies. With this acquisition, Rockwood became the world's largest specialty chemicals producer with an estimated annual turnover of EUR 2.5 billion.
- GlaxoSmithKline is investing EUR 94.3 million in Dresden to produce additional influenza vaccine.
- Pfizer plans to invest in a production site for an osteoporosis drug in the amount of EUR 53 million .

Products of Major Intermediates Manufacturers in Germany/Europe:

BASF produces synthesis components, ionic liquids, catalyzers, boron specialties for selective reductions, hydroborations, Suzuki couplings, hydroxylamines, alkoholates, alkali metals. http://www.pharma-solutions.basf.de/(kz5dap45gmq1k5ahbwvi2sbd)/exclusive_custom_synthesis.aspx?GrpID=64

DSM, the world's largest producer of penicillin, is still under price pressure as a result of Chinese competition producing large amounts of low-price antibiotics.

Lanxess offers a wide portfolio of basic/fine chemicals, including phosgenation, high-pressure hydrogenation, carbonylation, fluorination, synthesis components. Lanxess has recently invested in technologies for homogeneous catalysis reactions (Palladium catalyzed C-N- and C-O coupling reactions).
http://www.fine.lanxess.com/fch/en/info/brochures/

BASF and Swiss Solvias cooperate in the field of ligands. BASF focuses on the biocatalysis and the symmetric hydrogenation of optically active intermediates for the life-science industry while Solvias is concentrating on asymmetric hydrogenation and chiral Solvias ligands. Solvias mainly operates as a CMO, supplying customer-exclusive intermediates. http://www.solvias.com/english/contact/index.html

Degussa is further expanding its Chinese activities. It already has 17 facilities, 12 of which are production sites. Degussa offers chemical and enzymatic chiral technologies for advanced pharmaceutical intermediates and APIs such as peptidic LHRH-antagonists, ACE-inhibitors, high potency drugs, and oligos. http://www.degussa4pharma.com/

Rhodia: Chiral building blocks, fluorinated products, diphenol products, phosphorous products, nitro and amino products. http://www.rhodia-pharmasolutions.com

Key Contacts

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Trade Publications

In Germany, trade publications are major vehicles for product promotion. The following German-language publications are of major interest:

CHEMISCHE RUNDSCHAU
Internet: www.chemische-rundschau.ch
E-mail: redaktion@chemische-rundschau.ch

CHEMANAGER
Internet: www.chemanager.de
E-mail: chemanager@gitverlag.com

Opportunities for Profile Building / Trade Shows:

German and European trade shows are international platforms for U.S. firms seeking to network with German and international buyers/distributors and to assess their competitors' lines and market situation. Upcoming trade shows in related sectors:

ILMAC, Basel, September 25-28, 2007:
The biennial ILMAC presents environmental and process technology in pharmaceuticals, chemicals and biotechnology." Last ILMAC hosted 513 exhibitors and 5,346 attendees.
http://www.ilmac.ch/ca/cc/ss/?lang=eng
CPhI, Madrid, November 1-3, 2005 / Paris, October 3-5, 2006:
The international CPhI show focuses on pharmaceutical ingredients and related industries. In 2004 it presented 1,232 exhibitors attracting 11,482 visitors.
http://www.cphi.com/content/aboutus.aspx?menuid=b130d430-6918-47d6-8b3d-2fc010e04da5
ChemSpec Europe, Geneva, June 14-15, 2006:
Europe's speciality chemicals event, also presenting intermediate applications in: Pharmaceuticals, agrochemicals, biotechnology, contract manufacturing etc. In 2005, 419 exhibitors participated in the event attracting 6,314 attendees.
http://www.chemspeceurope.com/index.shtml
Biotechnica, Hanover, October 18-20, 2005/ Hanover, October 9-11, 2007:
The Biotechnica 2005 expects 900 exhibitors and approximately 12,000 attendees.
http://www.bio-pro.de/en/life/veranstaltungen/01183/index.html

For More Information

The U.S. Commercial Service Germany can be contacted via e-mail at: dusseldorf.office.box@mail.doc.gov, website: http://www.buyusa.gov/germany/en/.

You can locate your nearest U.S. Export Assistance Center, as well as Commercial Service offices overseas by visiting www.buyusa.gov.